PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 January 1999 (07.01.99)	
International application No. PCT/ES98/00145	**Applicant's or agent's file reference** 98133
International filing date (day/month/year) 25 May 1998 (25.05.98)	**Priority date** (day/month/year) 29 May 1997 (29.05.97)
Applicant MONSALVATJE LLAGOSTERA, Montserrat et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   03 December 1998 (03.12.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

J. Leitao

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

09/424673

20 SEP. 1999

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

CARPINTERO LOPEZ Francisco
HERRERO & ASOCIADOS, S.L.
Alcalá 21
E - 28014 Madrid
ESPAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.09.99
Applicant's or agent's file reference: 98133	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES98/00145	25/05/1998	29/05/1997

Applicant
ESTEVE QUIMICA, S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel.+49 89 2399-8012

Form PCT/IPEA/416 (July 1992)

EL 386266139US

09/424673

REC'D 20 SEP 1999

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
98133		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES98/00145	25/05/1998	29/05/1997
International Patent Classification (IPC) or national classification and IPC C07D217/26		
Applicant ESTEVE QUIMICA, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/12/1998	16.09.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Howarth, C Telephone No. +49 89 2399 8207

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/ES98/00145

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-18	as originally filed				

Claims, No.:

15-22	as originally filed				
1-14	as received on	16/07/1999	with letter of	12/07/1999	

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re: I

In the new structural formulae of claim 1 the oxo groups have been omitted, for which no basis can be found.

The amendment to claim 1 part e) also appears to have no basis since the range of 40-50 °C appears to relate only to the ethyl formate and methyl acetate solvates (see p.9).

No basis can be found in the originally filed documents for the amendment to claim 9.

This report has therefore been established as if the above amendments had not been made.

Re: V

1. Cited Documents

D1 = US-A-4 344 949
D2 = US-A-4 761 479
D3 = BE-A-0 892 552

The written opinion referred to the above documents in the order they are given in the International Search Report. The numbering given above (which is retained) erroneously exchanged the first two documents, thus US-A-4 761 479 was referred to as D1. The discrepancy appears to have been detected by the Applicant as evidenced by the comment regarding inventive step (To point g).

2. Novelty

The process of the application differs from that of:
- **D2** in that the second solvate may not be formed using acetonitrile.
- **D1** and D3 in that one solvate is converted into another solvate.

The specific solvates of claims 18-22 are not disclosed in D1-D3.

Novelty is therefore acknowledged.

3. Inventive Step

a. The closest prior art is given by **D2** which discloses a similar process for the synthesis of compounds of formula (I) differing essentially only in the choice of solvents used to form the first and second solvates.

b. The problem underlying the invention would appear to be one of providing an alternative process for the synthesis of the hydrochloride salt of quinapril which overcomes the drawbacks of the prior art processes (see p.4).

c. The main drawback referred to regarding D2 is the use of the carcinogenic solvent acetonitrile.

d. The proposed solution involves the formation of a solvate with a "solvent belonging to class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying without degrading the quinapril hydrochloride".

e. If the problem is one of avoiding the use of acetonitrile, then the solution, namely of not using acetonitrile, but using a different suitable solvent, is considered obvious and an inventive step cannot be acknowledged. The definition is further clearly a definition by the effect to be achieved.

f. Regarding the comments of the Applicant's letter of 12.7.99 with respect to D2 (point 1.3.1 part 2.) : The formation of the hydrochloride salt from the benzyl ester involving H_2 and Pd/C cannot contribute to an inventive step, since this type of debenzylation is already known (e.g. from D1, Example 1). Further, the xylene solvate is isolated (see D2, column 4, line 20).

g. Since it has not been shown that using toluene to form the first solvate as opposed to xylene, as in D2, is technically relevant or that using ethyl formate or methyl acetate as opposed to acetonitrile results in any surprising effect an inventive step cannot be acknowledged for the intermediates either.

Re: VIII

1. Clarity

a. The term "slightly greater" in claim 9 is unclear. Also, the phrasing "can be" has no limiting effect on the scope of the claim. There appears to be no indication in the description of precisely what is meant by the term.

b. The term "hydrogenolysis" appears to be used to mean catalytic debenzylation in conjunction with hydrochloride salt formation. This is not immediately clear.

c. The term "class 3 solvent" is not clear in and of itself.

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SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(51) Clasificación Internacional de Patentes 6 : C07D 217/26

A1

(11) Número de publicación internacional: **WO 98/54149**

(43) Fecha de publicación internacional: 3 de Diciembre de 1998 (03.12.98)

(21) Solicitud internacional: PCT/ES98/00145

(22) Fecha de la presentación internacional: 25 de Mayo de 1998 (25.05.98)

(30) Datos relativos a la prioridad:
P 9701169 29 de Mayo de 1997 (29.05.97) ES

(71) Solicitante *(para todos los Estados designados salvo US)*: ESTEVE QUIMICA, S.A. [ES/ES]; Avenida Mare De Déu de Montserrat, 12, E-08024 Barcelona (ES).

(72) Inventores; e

(75) Inventores/solicitantes *(sólo US)*: MONSALVATJE LLAGOSTERA, Montserrat [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES). BARTRA SANMARTÍ, Martí [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES). TOMAS NAVARRO, Jaime [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES). PUIG TORRES, Salvador [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES).

(74) Mandatario: CARPINTERO LOPEZ, Francisco; Herrero & Asociados, S.L., Alcalá, 21, E-28014 Madrid (ES).

(81) Estados designados: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, Patente ARIPO (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Patente euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

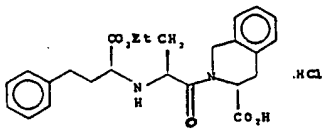
Publicada

Con informe de búsqueda internacional.

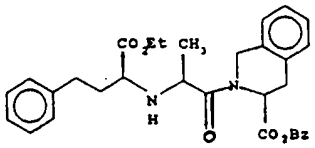
Antes de la expiración del plazo previsto para la modificación de las reivindicaciones, será publicada nuevamente si se reciben modificaciones.

(54) Title: PROCESS FOR OBTAINING QUINAPRYL HYDROCHLORIDE AND SOLVATES USEFUL FOR ISOLATING AND PURIFYING QUINAPRYL HYDROCHLORIDE

(54) Título: PROCEDIMIENTO PARA LA OBTENCIÓN DE QUINAPRIL CLORHIDRATO Y SOLVATOS UTILES PARA EL AISLAMIENTO Y PURIFICACIÓN DE QUINAPRIL CLORHIDRATO



(I)



(II)

(57) **Abstract**

The process for obtaining quinapryl hydrochloride (I) comprises the following steps: a) hydrogenolysis of quinapryl benzyl ester (II) by treatment in an alcoholic solvent, with hydrochloric acid or with a solution of hydrogen chloride in isopropanol and hydrogenation; b) removing the solvent; c) addition of toluen to precipitate the quinapryl hydrochloride as toluen solvate; d) treating said solvate with a solvent of class 3 to form a solvate of quinapryl hydrochloride from which it can be dry-removed without degradation; and e) drying the solvate of step b) to yield (I). These solvates are useful to isolate and purify (I), an antihypertensive agent.

(57) **Resumen**

El procedimiento para obtener quinapril clorhidrato (I) comprende las etapas de: a) hidrogenolisis del éster bencílico del quinapril (II) por tratamiento en un disolvente alcohólico, con ácido clorhídrico o con una disolución de cloruro de hidrógeno en isopropanol e hidrogenación; b) retirada del disolvente; c) adición de tolueno para precipitar el quinapril clorhidrato como solvato de tolueno; d) tratamiento de dicho solvato con un disolvente de la Clase 3 que forma un solvato de quinapril clorhidrato del que se puede eliminar por secado sin degradarlo; y e) secado del solvato de la etapa d) para rendir (I). Estos solvatos son útiles para aislar y purificar (I), un agente antihipertensivo.

UNICAMENTE PARA INFORMACION

Códigos utilizados para identificar a los Estados parte en el PCT en las páginas de portada de los folletos en los cuales se publican las solicitudes internacionales en el marco del PCT.

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PROCEDIMIENTO PARA LA OBTENCIÓN DE QUINAPRIL CLORHIDRATO Y SOLVATOS UTILES PARA EL AISLAMIENTO Y PURIFICACIÓN DE QUINAPRIL CLORHIDRATO

CAMPO DE LA INVENCIÓN

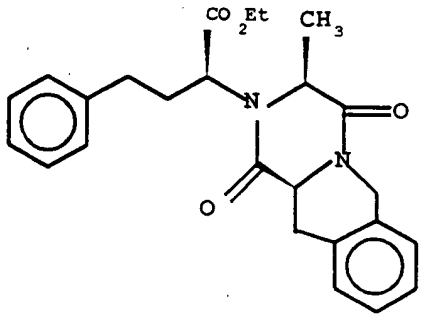
Esta invención se refiere a un procedimiento para la obtención de quinapril clorhidrato, así como a nuevos solvatos de quinapril clorhidrato, obtenidos mediante el empleo de disolventes de la Clase 3, de los que se puede eliminar el disolvente por secado sin degradación del producto, útiles para el aislamiento y la purificación del quinapril clorhidrato. El procedimiento puede ser desarrollado a escala industrial.

ANTECEDENTES DE LA INVENCIÓN

Quinapril es la denominación común internacional del compuesto químico de nombre ácido (S)-2-[(S)-N-[(S)-1-etoxi-carbonil-3-fenilpropil]-L-alanil]-1,2,3,4-tetrahidro-3-isoquinolin-carboxílico]. El quinapril y sus sales aceptables farmacéuticamente son agentes antihipertensivos que actúan como inhibidores de la enzima conversora de la angiotensina (ECA).

La primera descripción del quinapril aparece en la patente norteamericana nº US 4.344.949 donde se describe además su preparación a partir del éster etílico del ácido (S,S)-α-[(1-carboxietil)amino]fenilbutanoico y del éster bencílico o t-butílico del ácido (S)-1,2,3,4-tetrahidro-3-isoquinolin-carboxílico por condensación peptídica con diciclohexil-carbodiimida (DCC) y activación con hidroxibenzotriazol. El éster bencílico o t-butílico del quinapril obtenido es desprotegido por hidrogenación catalítica o por tratamiento con ácido trifluoroacético y el aislamiento final del quinapril se efectúa (a escala de laboratorio) por precipitación con éter etílico y por liofilización de una solución acuosa. El aislamiento del quinapril es muy delicado ya que este producto se degrada muy fácilmente por ciclación intramolecular para dar una

dicetopiperazina de fórmula



tanto en solución orgánica o acuosa como en estado sólido.

El procedimiento descrito en dicha patente US 4.344.949 presenta los inconvenientes propios del empleo de DCC, puesto que las condensaciones efectuadas en presencia de DCC rinden bastantes impurezas, con la consiguiente bajada de rendimiento (61%), debe separarse la diciclohexilurea resultante, y, además, las carbodiimidas son las responsables de alergias muy fuertes.

El quinapril clorhidrato es la sal habitualmente utilizada en la elaboración de medicamentos que comprenden quinapril.

La patente norteamericana nº US 4.761.479 menciona que la obtención y purificación del quinapril clorhidrato viene dificultada por su fácil degradación en subproductos, principalmente la dicetopiperazina antes mostrada. Dicha patente US 4.761.479 describe un procedimiento de obtención de quinapril clorhidrato que comprende la desprotección del éster t-butílico del quinapril con HCl gas en ácido acético, el aislamiento del producto por precipitación tras adición de xileno y destilación a vacío, y la purificación del quinapril clorhidrato por cristalización con acetonitrilo para dar

un solvato de acetonitrilo cristalino. El disolvente de dicho solvato puede eliminarse por secado en una estufa de vacío sin degradar el quinapril clorhidrato. Sin embargo, el acetonitrilo es un disolvente de la Clase 2, definidos por la ICH [International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use] como "Carcinógenos no mutagénicos en animales o posibles causantes de otras toxicidades irreversibles tales como neurotoxicidad, teratogénesis o bien sospechosos de toxicidades reversibles significantes y, por tanto, su proporción tiene que estar limitada". En el caso del acetonitrilo la ICH recomienda un límite no superior a las 250 ppm (0,025%). Este límite es difícil de conseguirse a escala industrial debido a la poca estabilidad del producto.

La patente belga nº BE 892.552 describe otro procedimiento de preparación del quinapril clorhidrato a partir del ácido (S,S)-α-[(1-carboxietil)amino]fenilbutanoico por activación con 1,1'-carbonildiimidazol que rinde un N-carboxianhidrido que reacciona *in situ*, sin aislamiento previo, con el éster bencílico del ácido (S)-1,2,3,4-tetrahidro-3-isoquinolin-carboxílico para dar el correspondiente éster bencílico de quinapril con un rendimiento del 56%. El quinapril protegido como éster bencílico resultante se hidrogena a continuación en presencia de Pd/C y se trata con ácido clorhídrico para rendir el quinapril clorhidrato, que se purifica por cromatografía y liofilización, con un rendimiento muy bajo (37%). Esta vía de síntesis también se menciona de forma genérica en la patente española ES 2.004.804 pero sin dar condiciones específicas, ni rendimientos, ni descripción de propiedades de los productos obtenidos. En particular, no se ejemplifica la síntesis del quinapril clorhidrato.

En general, todos los procedimientos descritos para la obtención del quinapril clorhidrato se caracterizan por su dificultad o por sus bajos rendimientos. Solamente la

patente US 4.761.479 describe un procedimiento para el aislàmiento industrial, y su purificación, del quinapril clorhidrato a partir del éster t-butílico del quinapril. Sin embargo, dicho procedimiento tiene el inconveniente de usar un disolvente carcinógeno (acetonitrilo) para obtener el solvato correspondiente.

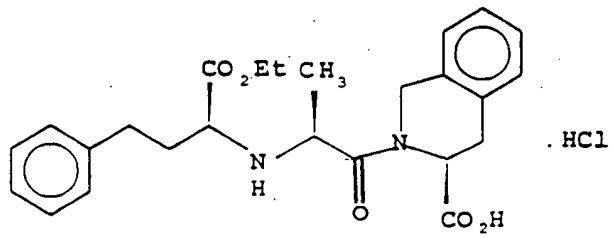
Por consiguiente, existe la necesidad de disponer de un procedimiento de obtención y purificación de quinapril clorhidrato, que pueda ser ejecutado a nivel industrial, que supere los inconvenientes previamente mencionados. Para obtener y purificar quinapril clorhidrato con un rendimiento elevado la invención propone la precipitación de dicho producto en forma de un solvato de tolueno. Por consiguiente, un objeto de esta invención lo constituye un procedimiento para la obtención de quinapril clorhidrato que comprende su aislamiento como solvato de tolueno.

Por otra parte, los solvatos de quinapril clorhidrato, compuestos útiles para la purificación de dicho producto, son, en general, productos de los que no se puede eliminar el disolvente por secado sin degradar parcialmente el quinapril clorhidrato. El único solvato de quinapril clorhidrato conocido que puede ser secado sin que se degrade el producto es el solvato de acetonitrilo, pero dicho solvato se ha obtenido con un disolvente carcinógeno. Para superar estos inconvenientes la invención proporciona unos solvatos de quinapril clorhidrato que pueden ser secados para eliminar el disolvente sin degradar el quinapril clorhidrato y que han sido obtenidos mediante el empleo de disolventes no carcinógenos. Por consiguiente, un objeto adicional de esta invención lo constituyen nuevos solvatos de disolventes pertenecientes a la Clase 3 de quinapril clorhidrato de los que puede eliminarse el disolvente por secado sin degradación del quinapril clorhidrato. Los disolventes de la Clase 3 se definen, según la ICH, como "Disolventes con bajo potencial tóxico para el hombre, no siendo necesario establecer un límite de exposición basado

en criterios de salud. Los disolventes de la Clase 3 tienen una EDP (Exposición Diaria Permitida) igual o superior a 50 mg poer día".

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

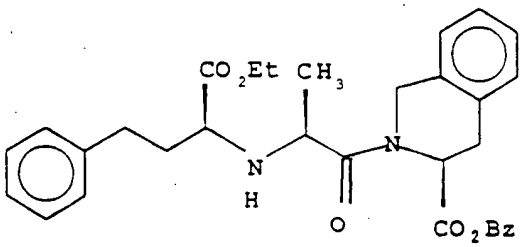
La invención proporciona un procedimiento para la obtención de quinapril clorhidrato de fórmula (I)



(I)

que comprende las etapas de:

a) hidrogenolisis del éster bencílico del quinapril (II)



(II)

donde Bz es el radical bencilo;

b) retirada del disolvente utilizado en la etapa a);

c) adición de tolueno para precipitar el quinapril clorhidrato como solvato de tolueno;

d) tratamiento del solvato de tolueno del quinapril

clorhidrato con un disolvente perteneciente a la Clase 3, capaz de formar un solvato de quinapril clorhidrato del que se puede eliminar dicho disolvente por secado en estufa sin degradar el quinapril clorhidrato; y

e) secado del solvato obtenido en la etapa d) para rendir el quinapril clorhidrato (I).

El éster bencílico del quinapril (II) es un producto conocido que puede obtenerse por cualquiera de los procedimientos descritos en las patentes US 4.344.949 y BE 892.552, antes mencionadas así como en las patentes EP 135181 y EP 135182 donde se describe, de forma genérica, la obtención del quinapril protegido como éster bencílico a partir del ácido (S,S)-α-[(1-carboxietil)amino]fenilbutanoico por activación con anhidridos alquenofosfónicos.

La reacción de hidrogenolisis del éster bencílico del quinapril (II) se puede llevar a cabo en un disolvente alcohólico, tal como etanol o isopropanol, con ácido clorhídrico concentrado o con una disolución de cloruro de hidrógeno en isopropanol, hidrogenación con hidrógeno gas a una presión comprendida entre aproximadamente 10^4 Pa (0,1 bar) y aproximadamente 2 x 10^5 Pa (2 bar), a una temperatura comprendida entre 10 y 40ºC, en presencia de un catalizador de hidrogenación apropiado, por ejemplo, Pd/C.

En una realización particular, la reacción de hidrogenolisis se efectúa utilizando etanol como disolvente, ácido clorhídrico concentrado, una presión de 10^5 Pa (1 bar) y temperatura ambiente. En otra realización particular, la reacción de hidrogenolisis se lleva a cabo utilizando isopropanol como disolvente, una disolución de cloruro de hidrógeno en isopropanol, una presión de 2 x 10^5 Pa (2 bar) y una temperatura de 30ºC aproximadamente.

La relación molar entre el éster bencílico del quinapril (II) y el ácido clorhídrico puede ser igual o ligeramente superior a la estequiométrica, preferentemente dicha relación molar es estequiométrica ya que, en caso de

un gran defecto de ácido clorhídrico el quinapril tiende a ciclarse para formar la dicetopiperazina antes mostrada, mientras que en caso de exceso de ácido se produce una descomposición del quinapril clorhidrato y del propio éster bencílico del quinapril.

En general, el ácido clorhídrico se añade a temperatura ambiente y la reacción entre el ácido clorhídrico y el éster bencílico del quinapril (II) es prácticamente inmediata, del orden de minutos.

Puesto que la disolución del éster bencílico del quinapril clorhidrato en isopropanol es más estable que la disolución de la base libre y, por otra parte, teniendo en cuenta la inestabilidad del éster bencílico del quinapril (II), la manera más fiable de conservar ese producto durante cortos periodos de tiempo es manteniéndolo como clorhidrato en disolución de isopropanol.

Una vez finalizada la hidrogenación, se retira el catalizador, por ejemplo, por filtración, y el disolvente utilizado, etanol o isopropanol, se retira, por ejemplo, por destilación a vacío, a una temperatura inferior a 40ºC, pues a temperaturas superiores la ciclación del producto para formar la dicetopiperazina es cuantitativamente más importante, y se añade tolueno. Estas operaciones de retirada del disolvente y adición de tolueno pueden repetirse un número variable de veces. A continuación, la masa de la reacción se deja a temperatura ambiente para que precipite el quinapril clorhidrato en forma de solvato de tolueno.

En una realización particular, para obtener el solvato de tolueno del quinapril clorhidrato a partir de la disolución del crudo en el disolvente utilizado (etanol o isopropanol), dicha disolución se destila hasta un volumen determinado de aproximadamente 1,6 ml/g de éster bencílico de quinapril y entonces se añade una cantidad de tolueno de aproximadamente 2,25 ml de tolueno por gramo de éster bencílico de quinapril. Seguidamente se vuelve a destilar hasta el mismo volumen anterior y añade la misma

cantidad de tolueno. Operando en estas condiciones, precipita el quinapril clorhidrato en forma de solvato de tolueno en un periodo de tiempo comprendido entre 20 y 60 minutos. Siguiendo este procedimiento de precipitación del solvato de tolueno, utilizando isopropanol como disolvente se obtiene un mayor rendimiento que utilizando etanol, lo que puede en gran parte ser debido a que el quinapril clorhidrato es más soluble en etanol que en isopropanol.

El solvato de tolueno de quinapril clorhidrato precipitado se filtra y se seca, obteniéndose un rendimiento comprendido entre el 85% y el 90% aproximadamente. Este solvato es un intermedio muy apropiado para la purificación posterior del quinapril clorhidrato según el procedimiento propuesto por esta invención. Las características espectroscópicas (IR, ^{1}H-RMN y ^{13}C-RMN) de este solvato de tolueno se recogen en el Ejemplo 2.1. Los intentos realizados para eliminar el tolueno por secado de dicho solvato sin degradar el quinapril clorhidrato resultaron infructuosos.

A continuación, el solvato de tolueno del quinapril clorhidrato se trata con un disolvente perteneciente a la Clase 3, es decir, no tóxico, no carcinógeno, por ejemplo, formiato de etilo o acetato de metilo, a una temperatura comprendida entre 40ºC y 45ºC, durante un periodo de tiempo comprendido entre 1 y 2 horas, y posteriormente se enfría a una temperatura comprendida entre 20ºC y 25ºC, durante un periodo de tiempo comprendido entre 1 y 2 horas, para formar el correspondiente solvato bien de formiato de etilo o bien de acetato de metilo, que se filtra y se seca, con un rendimiento en cualquiera de los casos de aproximadamente el 95%. Estos solvatos se pueden secar en estufa, para eliminar el disolvente, sin degradar el quinapril clorhidrato. Estos solvatos son intermedios clave para la obtención del quinapril clorhidrato de elevada pureza (99,8%) según el procedimiento objeto de esta invención. Las características espectroscópicas (IR, ^{1}H-RMN y ^{13} C-RMN) y de difracción de Rayos X de estos

solvatos se recogen en los Ejemplos 2.2 y 2.3.

El secado de los solvatos de formiato de etilo o de acetato de metilo del quinapril clorhidrato así obtenidos para rendir el quinapril clorhidrato se puede efectuar en estufa, por ejemplo en estufa de vacío, a una temperatura comprendida entre 40 y 50ºC aproximadamente, durante un periodo de tiempo comprendido entre 12 y 24 horas dependiendo de la cantidad de solvato a secar. El quinapril clorhidrato resultante, cuyas características espectroscópicas (IR, ^{1}H-RMN y ^{13}C-RMN), de rotación óptica y de difracción de Rayos X se recogen en el Ejemplo 2.4 es un producto amorfo cuyo difractograma de Rayos X presenta pocos picos y con intensidad baja, por lo que *a priori* es un producto amorfo.

La hidrogenación del producto resultante tras la adición del ácido clorhídrico o la disolución de cloruro de hidrógeno en isopropanol en la etapa a) se puede efectuar sin aislamiento previo del intermedio formado. Asimismo, la masa de reacción resultante de la hidrogenolisis puede ser sometida a destilación para retirar el disolvente utilizado en la etapa a) sin aislamiento del producto formado.

En una realización particular y preferida de la invención, el éster bencílico del quinapril se obtiene por condensación del N-carboxianhidrido de la N-[1-(S)-etoxicarbonil-3-fenilpropil]-L-alanina y del éster bencílico del ácido (S)-1,2,3,4-tetrahidro-3-isoquinolincarboxílico. El éster bencílico del quinapril (II) resultante, sin aislar, se somete al tratamiento previamente descrito. El N-carboxianhidrido puede obtenerse por el procedimiento descrito, por ejemplo, en la patente BE 892.552.

Los siguientes ejemplos sirven para ilustrar formas particulares de realización del procedimiento objeto de la invención sin que deban ser considerados como limitativos del alcance de la misma. Todos los análisis de difracción de Rayos X están hechos por el método del polvo cristalino

(λ = 1,5419 Å), las preparaciones de las muestras se han hecho sobre un stándar en seco.

Material del ánodo: cobre
Longitud de onda, λ_1 (Å) = 1,54060
Longitud de onda, λ_2 (Å) = 1,54439
Angulo inicial (2θº): 6,025
Angulo final (2θº): 39,985
Valor d inicial (Å) = 14,65735
Valor d final (Å) = 2,25302

EJEMPLO 1

Preparación del éster bencílico del ácido (S,S,S) 2-[2-[(1-(etoxicarbonil)-3-fenilpropil)amino]1-oxopropil]-1,2,3,4-tetrahidro-3-isoquinolincarboxílico [éster bencílico del quinapril (II)]

Se suspenden 51,3 g (0,12 moles) de para-toluensulfonato del éster bencílico del ácido (S)-1,2,3,4-tetrahidro-isoquinolin-3-carboxílico, en 150 ml de tolueno. Con agitación, se añaden 200 ml de solución de bicarbonato sódico al 10% y se agita la mezcla hasta disolución total. Se decanta y se separa la fase orgánica que se vuelve a lavar con 100 ml de solución al 10% de bicarbonato sódico, y a continuación se seca con sulfato sódico y se filtra. A temperatura ambiente, se añaden sobre esta solución toluénica 36,0 g (0,12 moles) del N-carboxianhidrido de la N-[1-(S)-etoxicarbonil-3-fenilpropil]-L-alanina, disuelto en 75 ml de tolueno, en 1 hora. La reacción está acabada al cabo de unas 4 horas tras la adición de dicho N-carboxianhidrido. La fase toluénica se lava con solución de hidróxido sodico al 5%, y luego agua, y se destila con vacío el disolvente hasta obtener un aceite, 62 g (Rendimiento: 98%) que es el éster bencílico del quinapril.

Tras formar el maleato, éste se caracteriza por:

- HPLC: el producto es de una pureza del 99,3%
- Valoración: 100,2%
- $[\alpha]^D$ = -12,93º (2%, metanol)

- IR (KBr) (ν, cm^{-1}): 3520, 3050, 2980, 1746, 1656, 1603, 1455, 1347, 1211, 1010, 751, 697.

Este compuesto en disolución es una mezcla de dos rotámeros. La distribución de rotámeros se observa en algunos casos en los espectros de resonancia magnética nuclear (RMN) de protón y de carbono 13.

^{1}H-RMN ($CDCl_3$, 300 MHz) (δ(ppm)): 10,40 (b. ancha, 3H); 7,40-7,00 (m, 14 H); 6,29 (s, 2H); 5,43 (dd, J_1 = 3,9 Hz, J_2 = 5,9 Hz, 1H); 5,02 (m, 2H); 4,60 (m, 2H); 4,44 (q, $J_1 = J_2 = J_3$ = 7,1 Hz, 1H); 4,23 (m, 2H); 3,77 (t_{min}), 3,72 (t, J_1 = 6,3 Hz, 1H); 3,45-3,05 (m, 2H); 2,85-2,65 (m, 2H); 2,30-2,15 (m, 2H); 1,6 (d_{min}, J_1 = 6,8 Hz), 1,45 (d, J_1 = 6,9 Hz), 3H; 1,28 (t, $J_1 = J_2$ = 7,2 Hz, 3H).

^{13}C-RMN ($CDCl_3$, 75 MHz) (δ(ppm)): 170,4 (min), 170,1, 169,7 (min), 169,2 (min), 169,1, 139,6 (min), 139,5, 135,3, 135,1 (min), 134,5, 131,8, 131,3 (min), 130,9 (min), 130,7, 128,6, 128,5, 128,4, 128,3, 128,1, 128,0, 127,9, 127,8, 127,7, 127,4, 127,3, 126,6, 126,5, 126,4, 126,1, 67,9 (min), 67,2, 62,6, 62,4 (min), 59,5 (min), 58,6, 54,7 (min), 54,5 (min), 53,5, 52,6, 45,2, 44,5 (min), 32,4 (min), 32,1, 31,3 (min), 31,2, 30,5, 16,8 (min), 15,6, 14,0 (min), 13,9.

EJEMPLO 2

Preparación del ácido (S,S,S) 2-[2-[(1-(etoxicarbonil)-3-fenil-propil)amino]-1-oxopropil]-1,2,3,4-tetrahidroisoquinolin-3-carboxílico clorhidrato [Quinapril clorhidrato (I)]

2.1 Solvato de tolueno del quinapril clorhidrato

Se disuelven 62,0 g del éster bencílico del quinapril, obtenido según el Ejemplo 1, con 400 ml de etanol y 10 ml de ácido clorhídrico concentrado, se añaden 3,1 g de catalizador de Pd/C al 5% (pasta) y se hidrogena a temperatura ambiente y presión de 10^5 Pa (1 bar) durante 3 horas. Finalizada la hidrogenación, el catalizador se filtra, se destila con vacío la mayor parte del etanol y se añaden 150 ml de tolueno. A continuación, se vuelve a

destilar con vacío la mayor parte del disolvente y se añaden otros 150 ml de tolueno. Posteriormente, se deja a temperatura ambiente, con lo que va precipitando un sólido que se filtra y se seca a vacío a 40ºC. Se obtuvieron 58,5 g (Rendimiento: 88%) de un producto que corresponde al solvato de tolueno del quinapril clorhidrato.

IR (KBr) (ν, cm^{-1}): 3520, 3026, 3003, 2928, 2802, 1755, 1742, 1711, 1646, 1558, 1538, 1495, 1455, 1203, 758, 737.

Este compuesto en disolución es una mezcla de dos rotámeros. La distribución de rotámeros se observa en algunos casos en los espectros de resonancia magnética nuclear de protón y del carbono 13.

^{1}H-RMN ($CDCl_3$, 300 MHz) (δ(ppm)): 7,20-7,00 (m, 14 H); 5,15 (t ancho), 4,97 ($ancho_{min}$), 1H; 4,82-4,45 (m, 3H); 4,35-4,05 (m, 2H); 3,90 (t ancho, 1H); 3,42-3,05 (m, 2H); 2,90-2,62 (m, 2H); 2,42-2,20 (m, 2H); 2,38 (s, 3H); 1,68 (d, J_1 = 6,2 Hz); 1,60 (d_{min}, J_1, = 6,2 Hz), 3H; 1,28 (t_{min}, J_1, = J_2, = 4,0 Hz); 1,22 (t, J_1 = J_2 = 4,0 Hz), 3H.

^{13}C-RMN ($CDCl_3$, 75 MHz) (δ(ppm)): 172,2, 171,4 (min), 169,2, 168,6, 168,2 (min), 168,0, 139,6 (min), 139,4, 137,8, 132,2, 131,4, 131,3, 131,2, 129,0, 128,6, 128,4, 128,2, 127,7, 127,1, 126,4, 126,3, 126,2, 125,2, 63,2 (min), 62,9, 59,1 (min), 58,9, 54,9 (min), 54,6 (min), 54,5, 53,1, 45,4, 44,1 (min), 31,9 (min), 31,4, 31,1, 31,0, 30,1 (min), 21,4, 16,2 (min), 15,2, 14,0 (min), 13,9.

2.2 Solvato de formiato de etilo de quinapril clorhidrato

Los 58,5 g de solvato de tolueno se agitan a 40-45ºC con 234 ml de formiato de etilo durante 2 horas y luego se enfría a una temperatura comprendida entre 20 y 25ºC durante dos horas más. El producto resultante se filtra y se seca en estufa de vacío a una temperatura de 30ºC durante cuatro horas para obtener 54 g de solvato de formiato de etilo de quinapril clorhidrato (Rendimiento:

95%).

IR (KBr) (ν, cm^{-1}): 3520, 3028, 3001, 2979, 2935, 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388, 1260, 1199, 756.

Este compuesto en disolución es una mezcla de dos rotámeros. La distribución de rotámeros se observa en algunos casos en los espectros de resonancia magnética nuclear de protón y del carbono 13.

^{1}H-RMN ($CDCl_3$, 300 MHz) (δ(ppm)): 10,00 (s ancho, 1H), 8,95 (s ancho, 1H), 8,02 (s, 1H); 7,15 (m, 9H); 5,15 (J_1 = J_2 = 5,6 Hz), 4,95 ($ancho_{min}$), 1H; 4,82-4,62 (m, 2H); 4,60-4,42 (m, 1H); 4,20 (q, $J_1 = J_2 = J_3$ = 7,0 Hz, 2H); 4,13 (q, $J_1 = J_2 = J_3$ = 7,0 Hz, 2H); 4,09-3,90 (m, 1H); 3,68 (q_{min}); 3,40-3,05 (m, 2H); 2,97-2,59 (m, 2H); 2,42-2,20 (m, 2H); 1,67 (d, J_1, = 7,0 Hz), 1,56 (d_{min}, J_1, = 7,0 Hz, 1H), 1,30 (t, $J_1 = J_2$ = 7,0 Hz), 1,18 ($J_1 = J_2$ = 7,0 Hz), 3H.

^{13}C-RMN ($CDCl_3$, 75 MHz) (δ(ppm)): 172,2, 171,3 (min), 169,2 (min), 168,6, 168,0, 161,0, 139,7 (min), 139,4, 132,2, 131,4 (min), 131,3 (min), 131,2, 128,5 (min), 128,4, 128,2, 127,2, 127,1, 126,3, 126,2, 126,1, 63,1 (min), 62,9, 59,9, 59,1 (min), 58,9, 58,2 (min), 54,8 (min), 54,6 (min), 54,5, 53,1, 45,4, 44,1 (min), 31,8 (min), 31,3, 31,1, 31,0, 30,8 (min), 30,1, 16,2 (min), 15,2, 14,1, 14,0 (min), 13,9.

Difracción de rayos X (polvo)

Solvato de formiato de etilo de quinapril clorhidrato

Angulo (2θº)	Intensidad relativa (%)
8,82	32,7
10,88	23,3
11,47	20,9
12,05	16,5
13,63	34,4
15,89	12,5
16,08	17,2
16,48	27,4
16,85	32,7
18,05	10,4
18,42	17,8
18,68	24,6
19,52	50,7
19,75	33,2
20,11	45,3
21,20	36,6
21,86	100,0
23,07	15,3
23,59	30,1
24,50	42,5
26,66	14,5
27,16	22,7
27,45	10,6
28,34	13,1
28,71	15,6
29,66	29,5
30,56	14,5
34,87	13,5

2.3 Solvato de acetato de metilo de quinapril clorhidrato

Siguiendo un procedimiento similar al descrito en el Ejemplo 2.2 pero sustituyendo el formiato de etilo por acetato de metilo se obtuvo el correspondiente solvato de acetato de metilo de quinapril clorhidrato (Rendimiento: 95%) que se caracteriza por los siguientes datos espectroscópicos.

IR (KBr) (ν, cm^{-1}): 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.

Este compuesto en disolución es una mezcla de dos rotámeros. La distribución de rotámeros se observa en algunos casos en los espectros de resonancia magnética nuclear de protón y de carbono 13.

^{1}H-RMN ($CDCl_3$, 300 MHz) (δ (ppm)): 10,10 (s ancho, 1H); 9,10 (s ancho, 1H); 7,21-7,06 (m, 9H); 5,14 (t, J_1 =

J_2 = 5,6 Hz, 1H); 4,80-4,67 (m, 2H); 4,57 (m, 1H); 4,21-4,19 (m, 2H); 4,16-3,89 (m, 1H); 3,66 (s, 3H); 3,41-3,00 (m, 2H); 2,72-2,62 (m, 2H); 2,34-2,29 (m, 2H); 2,05 (s, 3H); 1,67 (d, J_1 = 6,8 Hz), 1,57 (d_{min}, J = 6,8 Hz), 3H; 1,21 (t_{min}, J_1 = J_2 = 6,9 Hz); 1,17 (t, J = J_2 = 6,9 Hz), 3H.

^{13}C-RMN ($CDCl_3$, 75 MHz) (δ(ppm)): 172,2; 171,5 (min), 169,2 (min), 168,6, 168,3 (min), 168,1, 139,6 (min), 139,4, 132,2, 131,5 (min), 131,3 (min), 131,2, 128,6, 128,5, 128,4, 128,3 (min), 127,8 (min), 127,2, 126,4, 126,2 (min), 63,2 (min), 62,9, 58,9, 54,7 (min), 54,5, 53,2, 51,5, 45,4, 44,2 (min), 31,9 (min), 31,4, 31,1, 30,2, 20,6, 16,1 (min), 15,5, 14,0 (min), 13,9.

Difracción de rayos X (polvo)

Solvato de acetato de metilo de quinapril clorhidrato

Angulo (2θº)	Intensidad Relativa (%)
8,86	26,0
10,95	26,0
11,79	19,2
13,73	45,9
16,18	18,2
16,57	37,7
16,87	60,4
18,76	18,6
18,93	18,6
19,59	33,2
20,16	81,9
20,91	19,2
21,56	30,7
21,93	100,0
22,18	28,7
23,22	14,6
23,65	35,4
24,62	52,6
27,17	34,0
28,51	16,6
28,93	22,9
30,69	21,6
30,85	14,0

2.4 Quinapril clorhidrato

Los solvatos de formiato de etilo o de acetato de metilo de quinapril clorhidrato obtenidos según los Ejemplos 2.2 y 2.3 se pueden secar directamente en una estufa de vacío a una temperatura comprendida entre 40 y 50ºC durante un periodo de tiempo comprendido entre 12 y 14 horas, sin necesidad de aislarlos, para dar el quinapril clorhidrato que es un producto muy poco cristalino o amorfo, según pone de manifiesto su difractograma de Rayos X. De los 54 g de solvato de formiato de etilo de quinapril clorhidrato se obtienen 46 g de quinapril clorhidrato caracterizado por:

- HPLC: 99,8%
- $[\alpha]$= + 15,9º (2%, metanol)
- IR (KBr) (ν, cm^{-1}): 3415, 3059, 2982, 2936, 1740,

1651, 1541, 1497, 1473, 1455, 1443, 1386, 1379, 1207, 751, 702.

El quinapril clorhidrato en disolución es una mezcla de dos rotámeros. La distribución de rotámeros se observa en algunos casos en los espectros de resonancia magnética nuclear de protón y de carbono 13.

^{1}H-RMN (DMSO-d_6, 300 MHz) (δ(ppm)): 7,23 (m, 9H); 5,12 (m, 1H); 4,9-4,4 (m, 3H); 4,19 (m, 2H); 3,91 (m), 3,79 (m_{min}), 1H; 3,3-3,1 (m, 2H); 2,77-2,61 (m, 2H); 2,20 (m, 2H); 1,51 (d, J_1 = 6,4 Hz), 1,49 (d_{min}, J_1 = 5,1 Hz), 3H; 1,22 (t_{min}, $J_1 = J_2$ = 7,3 Hz), 1,17 (t, $J_1 = J_2$ = 7,3 Hz), 3H.

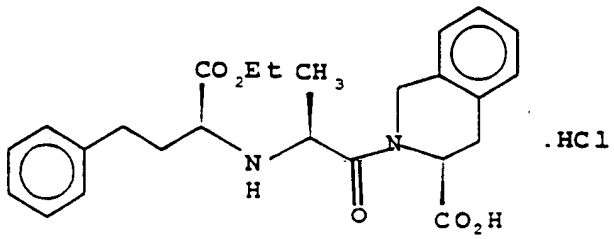
^{13}C-RMN (DMSO-d_6, 75 MHz) (δ (ppm)): 171,5, 171,4, 168,5, 140,2, 132,5, 132,4, 132,1 (min), 131,5 (min), 128,5, 128,4, 128,2, 128,1, 127,1, 126,7, 126,6, 126,3, 126,1, 125,4, 62,2 (min), 62,0, 57,4 (min), 57,3, 53,9 (min), 53,1 (min), 52,7, 52,0, 44,5, 43,6 (min), 31,3 (min), 30,8, 30,6 (min), 30,4, 30,0, 21,1 (min), 16,2 (min), 14,7, 13,9.

Difracción de Rayos X (polvo)
Quinapril clorhidrato

Angulo (2θº)	Intensidad relativa (%)
11,18	31,9
12,17	29,4
17,38	33,9
19,83	37,9
28,34	10,0

REIVINDICACIONES

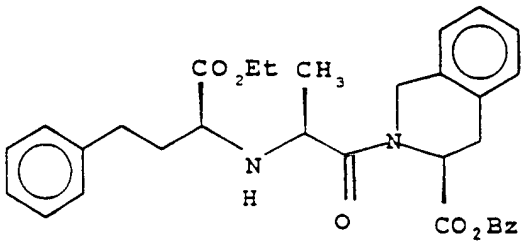
1. Un procedimiento para la obtención de quinapril clorhidrato de fórmula (I)



(I)

que comprende las etapas de:

a) hidrogenolisis del éster bencílico del quinapril (II)



(II)

donde Bz es el radical bencilo;

b) retirada del disolvente utilizado en la etapa a);

c) adición de tolueno para precipitar el quinapril clorhidrato como solvato de tolueno;

d) tratamiento del solvato de tolueno del quinapril clorhidrato con un disolvente perteneciente a la Clase 3, capaz de formar un solvato de quinapril clorhidrato del que se puede eliminar dicho disolvente por secado en estufa sin degradar el quinapril clorhidrato; y

e) secado del solvato obtenido en la etapa d) para

rendir el quinapril clorhidrato (I).

2. Un procedimiento según la reivindicación 1, en el que la reacción de hidrogenolisis del éster bencílico del quinapril (II) se lleva a cabo en un disolvente alcohólico, con tratamiento con ácido clorhídrico concentrado o con una disolución de cloruro de hidrógeno en isopropanol, e hidrogenación con hidrógeno gas en presencia de un catalizador de hidrogenación.

3. Un procedimiento según la reivindicación 2, en el que dicho disolvente alcohólico se selecciona entre etanol e isopropanol.

4. Un procedimiento según la reivindicación 2, en el que la hidrogenación se efectúa a una presión comprendida entre 10^4 Pa y 2 x 10^5 Pa.

5. Un procedimiento según la reivindicación 2, en el que la hidrogenación se efectúa a una temperatura comprendida entre 10 y 40ºC.

6. Un procedimiento según la reivindicación 2, en el que el catalizador de hidrogenación es Pd/C.

7. Un procedimiento según la reivindicación 2, en el que la reacción de hidrogenolisis del éster bencílico del quinapril (II) se lleva a cabo utilizando etanol como disolvente, ácido clorhídrico concentrado, una presión de 10^5 Pa (1 bar) y temperatura ambiente.

8. Un procedimiento según la reivindicación 2, en el que la reacción de hidrogenolisis del éster bencílico del quinapril (II) se lleva a cabo utilizando isopropanol como disolvente, una disolución de cloruro de hidrógeno en isopropanol, una presión de 2 x 10^5 Pa (2 bar) y una temperatura de 30ºC aproximadamente.

9. Un procedimiento según la reivindicación 2, en el que la relación molar entre el éster bencílico del quinapril (II) y el ácido clorhídrico es igual o ligeramente superior a la estequiométrica.

10. Un procedimiento según la reivindicación 1, en el que la retirada del disolvente utilizado en la etapa a) se efectúa por destilación a vacío.

11. Un procedimiento según la reivindicación 1, en el que el disolvente de la Clase 3 con el que se trata el solvato de tolueno del quinapril clorhidrato se selecciona entre formiato de etilo y acetato de metilo.

12. Un procedimiento según la reivindicación 1, en el que el tratamiento con el disolvente de la Clase 3 del solvato de tolueno del quinapril clorhidrato se efectúa a una temperatura comprendida entre 40ºC y 45ºC, durante un periodo de tiempo comprendido entre 1 y 2 horas, y posterior enfriamiento a una temperatura comprendida entre 20ºC y 25ºC, durante un periodo de tiempo comprendido entre 1 y 2 horas.

13. Un procedimiento según la reivindicación 1, en el que el solvato del disolvente de la Clase 3 del quinapril clorhidrato se selecciona entre el solvato de formiato de etilo del quinapril clorhidrato y el solvato de acetato de metilo del quinapril clorhidrato.

14. Un procedimiento según la reivindicación 1, en el que el solvato del disolvente de la Clase 3 del quinapril clorhidrato se seca en una estufa de vacío, a una temperatura comprendida entre 40ºC y 50ºC durante un periodo de tiempo comprendido entre 12 y 14 horas.

15. Un procedimiento según la reivindicación 1, en el que la hidrogenación del producto resultante tras la

adición del ácido clorhídrico o del cloruro de hidrógeno al éster bencílico del quinapril (II) en la etapa a) se efectúa sin aislamiento previo del intermedio formado.

16. Un procedimiento según la reivindicación 1, en el que el éster bencílico del quinapril (II) se obtiene por condensación del N-carboxianhidrido de la N-[1-(S)-etoxi-carbonil-3-fenilpropil]-L-alanina y del éster bencílico del ácido (S)-1,2,3,4-tetrahidro-3-isoquinolincarboxílico, seguido de hidrogenación en medio ácido.

17. Un procedimiento según la reivindicación 16, en el que el éster bencílico del quinapril (II) obtenido se utiliza sin aislamiento previo.

18. Un solvato de tolueno de quinapril clorhidrato caracterizado porque su espectro de infrarrojo presenta los siguientes picos:

IR (KBr) (ν, cm^{-1}): 3520, 3026, 3003, 2928, 2802, 1755, 1742, 1711, 1646, 1558, 1538, 1495, 1455, 1203, 758, 737.

19. Un solvato de formiato de etilo de quinapril clorhidrato caracterizado porque su difractograma de Rayos X presenta las siguientes características:

Difracción de rayos X (polvo)

Solvato de formiato de etilo de quinapril clorhidrato

Angulo (2θº)	Intensidad relativa (%)
8,82	32,7
10,88	23,3
11,47	20,9
12,05	16,5
13,63	34,4
15,89	12,5
16,08	17,2
16,48	27,4
16,85	32,7
18,05	10,4
18,42	17,8
18,68	24,6
19,52	50,7
19,75	33,2
20,11	45,3
21,20	36,6
21,86	100,0
23,07	15,3
23,59	30,1
24,50	42,5
26,66	14,5
27,16	22,7
27,45	10,6
28,34	13,1
28,71	15,6
29,66	29,5
30,56	14,5
34,87	13,5

20. Un solvato de formiato de etilo de quinapril clorhidrato según la reivindicación 19, caracterizado porque su espectro de infrarrojos presenta los siguientes picos:

IR (KBr) (ν, cm^{-1}): 3520, 3028, 3001, 2979, 2935, 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388, 1260, 1199, 756.

21. Un solvato de acetato de metilo de quinapril clorhidrato caracterizado porque su difractograma de Rayos X presenta las siguientes características:

Difracción de rayos X (polvo)

Solvato de acetato de metilo de quinapril clorhidrato

Angulo (2θº)	Intensidad Relativa (%)
8,86	26,0
10,95	26,0
11,79	19,2
13,73	45,9
16,18	18,2
16,57	37,7
16,87	60,4
18,76	18,6
18,93	18,6
19,59	33,2
20,16	81,9
20,91	19,2
21,56	30,7
21,93	100,0
22,18	28,7
23,22	14,6
23,65	35,4
24,62	52,6
27,17	34,0
28,51	16,6
28,93	22,9
30,69	21,6
30,85	14,0

22. Un solvato de acetato de metilo de quinapril clorhidrato según la reivindicación 21, caracterizado porque su espectro de infrarrojos presenta los siguientes picos:

IR (KBr) (ν, cm^{-1}): 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ES 98/00145

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D 217/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS, CIBEPAT, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4761479 A (GOEL) 2 August 1988 (02.08.88) claim 1	1
A	US 4344949 A (HOEFLE) 17 August 1982 (17.08.82) claims 1,4 and 10; example 2	1
A	BE 892552 A (USV PHARM. CORPORATION) 20 September 1982 (20.09.82) claim 13	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1998 (03.09.98)	21 September 1998 (21.09.98)
Name and mailing address of the ISA/ S.P.T.O. Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/ES 98/00145

Patent document cited in search report	Publication date	Patent familiy member(s)	Publication date
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		EP 285992 A	12.10.1988
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		AU 605555 A	17.01.1991
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		IN 156096 A	11.05.1985
		GB 2095252 A	29.09.1982
		FR 2502149 A	24.09.1982
		SE 8201654 A	20.09.1982
		DE 3209708 A	21.10.1982
		CH 658455 A	14.11.1986
		AU 8158482 A	23.09.1982
		NL 8201066 A	18.10.1982
		JP 57165355 A	12.10.1982

INFORME DE BÚSQUEDA INTERNACIONAL

Información relativa a miembros de familias de patentes

Solicitud internacional nº
PCT/ES 98/00145

Documento de patente citado en el informe de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
US 4761479 A	02.08.1988	KR 9607087 A	27.05.1996
		EP 285992 A	12.10.1988
		CA 1291999 A	12.11.1991
		AU 605555 A	17.01.1991
		JP 63258459 A	25.10.1988
US 4344949 A	17.08.1982	ZA 8106332 A	29.09.1982
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		JP 57088164 A	12.06.1982
BE 892552 A	20.09.1982	ZA 8201833 A	26.01.1983
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		DK 120982 A	20.09.1982
		IN 156096 A	11.05.1985
		GB 2095252 A	29.09.1982
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		SE 8201654 A	20.09.1982
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		CH 658455 A	14.11.1986
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		NL 8201066 A	18.10.1982
		JP 57165355 A	12.10.1982

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional nº
PCT/ES 98/00145

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

CIP[6] C07D 217/26
De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y la CIP.

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

Documentación mínima consultada (sistema de clasificación, seguido de los símbolos de clasificación)

CIP[6] C07D

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)

WPI, CAS, CIBEPAT, EPODOC

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones nº
A	US 4761479 A (GOEL) 02.08.1988 Reivindicación 1.	1
A	US 4344949 A (HOEFLE) 17.08.1982 Reivindicaciones 1, 4 y 10; ejemplo 2	1
A	BE 892552 A (USV PHARM. CORPORATION) 20.09.1982 Reivindicación 13	1

☐ En la continuación del recuadro C se relacionan otros documentos ☒ Los documentos de familia de patentes se indican en el anexo

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante.

"E" solicitud de patente o patente anterior pero publicada en la fecha de presentación internacional o en fecha posterior.

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada).

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio.

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada.

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención.

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado.

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia.

"&" documento que forma parte de la misma familia de patentes.

Fecha en que se ha concluido efectivamente la búsqueda internacional.	Fecha de expedición del informe de búsqueda internacional
3 Septiembre 1998 (03.09.1998)	21 SEP 1998 (21.09.98)
Nombre y dirección postal de la Administración encargada de la búsqueda internacional O.E.P.M. C/Panamá 1, 28071 Madrid, España. nº de fax +34 91 3495304	Funcionario autorizado MARTA OJANGUREN nº de teléfono + 34 91 3495474

Formulario PCT/ISA/210 (segunda hoja) (julio 1998)

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PCT Chapter II
MU DG 2

TELEFAX
CONFIRMATION

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Examining Authority

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Appln. No.	O/Ref.	Madrid
PCT/ES98/00145	98133 FP	12 July 1999

Re: International Patent Application No. PCT/ES98/00145
ESTEVE QUÍMICA, S.A..

Dear Sirs,

We refer to first Written Opinion drawn up by European Patent Office as International Preliminary Examining Authority dated 11 March 1999, which time limit for replying to the same was extended, and we hereby are lodging in the enclosed pages our comments to the cited Written Opinion.

TELEFAX
CONFIRMATION

Yours faithfully,
HERRERO & ASOCIADOS

EL 386266139US

REPLY TO THE FIRST WRITTEN OPINION ON THE PCT APPLICATION PCT/ES98/00145

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1. Comments on the novelty of the invention (Part 2 of the written opinion)

1.1. Object of the present application

The object of the present invention is the obtention of quinapril hydrochloride through a process which includes as an essential characteristic the isolation of the hydrochloride as a toluene solvate, and an essential object is the absence of use of acetonitrile due to the known toxicity of this solvent, as well as the absence of DCC (dicyclohexylcarbodiimide) during the obtention of the quinapril benzyl ester. The essensial steps of the process according to claim 1 are:

a) hydrogenolysis of the quinapril benzyl ester, preceded by the treatment with alcohol and hydrochloric acid,
b) removal of the solvent used,
c) addition of toluene to obtain the toluene solvate,
d) treatment of the toluene solvate with a class 3 solvent, and
e) drying of the toluene solvate.

1.2. Object of US-4,344,949 (D1)

D1 is a document cited in the present application a prior art. It refers to substituted acyl derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids and their peparations from 1,2,3,4-isoquinoline linked to substituted and N-protected amino acids. More specifically, quinapril is obtained by reaction of (S,S)-α-[1-(carboxyethyl)amino]phenylbutanoic acid ethyl ester with (S)-1,2,3,4-tetrahydro-3-isoquinolin carboxylic acid benzyl ester (example 7) or t-butyl ester (example 6) through condensation with DCC and activation with hydroxybenzotriazole. The process described in this patent includes therefore the use of acetonitrile for the condensation which involves many inconveniences during handling, and yield decrease and their derivatives are hazardous products. The use of acetonitrile is also considered therein as an appropriate aprotic solvent .

Only the compounds obtained and the method of treatment are claimed.

1.2.1. Comparative study of D2 and the present application

In addition to the differences found by the Examiner there exist also other essential ones as for example, the process of obtention of quinapril hydrochloride is completely different:

- In D1 the condensation occurs between two esters whereas in the present application the condensation occurs between an ester and the N-carboxyanhydride of N-[1-(S)-ethoxcarbonyl-3-phenylpropyl]-L-alanine;
- The condensation in D1 occurs in the presence of DCC and benzotriazole, whereas in the current application it occurs with the two compounds just dissolved in toluene;
- in D1, by the debenzylation stage of the quinapril benzyl ester, after filtering the catalyst, an amount of ether equivalent to ten volumes of the solution is added, whereas in the current application the solution is concentrated under vacuum and finally
- during the mentioned debenzylation stage, in D1 after the ether addition the product precipitates, whereas in the present application toluene is added, further the treatment with a class 3 solvent is carried out and the obtained solvate is dried.

According to the foregoing it is clearl that both processes are different and furthermore it is noteworthy to make a comment to section **3.a** of the written opinion, which is also related to D1: D1 does not disclose a process similar to that of the application in course, such as it was established trhough the preceding paragraphs, and therefore both processes are different not only because of the different solvents used, but also because of the use of different starting materials, different reaction conditions, and different products – as they are the toluene solvate, the ethyl formate solvate and the methyl acetate solvate –.

1.3. Object of US-4,761,479 (D2)

This patent refers to a new crystalline form of quinapril and to a new preparation process in large scale of quinapril as quinapril hydrochloride. D2 does not refer to the reactions previous to the formation of the hydrochloride, i.e, it is not an object of D2 to modify the synthesis of a quinapril diester, which is the starting compound of the claimed process. The process to obtain the crystalline quinapril hydrochloride comprises:

a) to solve and stir a quinapril diester into a reagent as HCl gas in glacial acetic acid (or trifluoroacetic acid, or methylene chloride),
b) to dilute the mixture with xylene and keep it under vaccum to obtain a solid,
c) to solve in acetonitrile,
d) to seed the solution and cool it,
e) to collect and dry the product at 25°C under vacuum between 1 and 24 hours to obtain the crystalline product and
f) to additionally dry under vacuum between 50°C and 60°C during 1-16 hours to obtain a product free of acetonitrile.

The preferred conditions for step a) include the use of HCl gas into glacial acetic acid with a reaction period of 6 hours and the preferred diester used is the 1,1-(S,S,S) dimethylester of quinapril. In step c) the preferred solvent used is acetonitrile at a temperature between 25 and 50°C; and for step (e) the drying occurs between 25°C and 50 °C.

This patent claims the crystalline quinapril hydrochloride and a process to obtain it, including the steps mentioned above, and there is a specific claim related to the use of acetonitrile in step c).

1.3.1. Comparative study of D2 and the present application

There are essential differences between both documents:

1. Concerning the object of the invention: the object of the present application is to avoid the use of acetonitrile and the use of DCC, and the object of D2 is to obtain a pure crystalline form and acetonitrile is even a preferred solvent for step (c) of the process, and
2. Concerning the process: the following important features inherent to D2 have no equivalent in the present application: a) D2 does not include a hydrogenolysis reaction with Pd/C, b) xylene is used instead of toluene and a xylene solvent is not isolated (what would correspond to the toluene solvate obtained in the present application).

According to the foregoing it is evident that both documents have different objectives and these are obtained through different means. The use of xylene instead of toluene does not deprive the present application of inventive height as the main object of D2 is not to prepare a xylene solvate; but a new crystalline form of quinapril hydrochloride. Furthermore, xylene behaves quite differently from toluene.

1.4. Object of BE-892552-A (D3)

BE-892552-A published on 20 September 1982 and cited in the present application as prior art, refers to new amido-amino acids, pharmaceutical compositions containing the same and to their preparation process.

The amido-amino acids are prepared according to different reaction types, among them, the formation reaction of an amide from an aminated compound containing the isoquinoline fragment of the final product and an acylating derivative of the acid containing the amino acid fragment of the final product. For the concrete case of quinapril this route involves the reaction of the N-carboxyanhydride (obtained from the (S,S)-α-[(1-ethoxycarbonyl)-amino]phenylbutanoic acid with the (S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid benzyl ester. The quinapril benzyl ester is hydrogenated with Pd/C and treated with HCl to yield the hydrochloride, which is purified through cromatography and lyophilization.

Example 1.C describes the formation of the 2-L-alanil-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid by addition of saturated hydrobromic acid into acetic acid.

Example 1.8.B of D3 describes the formation of quinapril hydrochloride and 1.8.A describes the formation of the quinapril benzyl ester ((S,S,S) isomer).

The quinapril hydrochloride, which obtention process is claimed, is one of the compounds included in D3 claims. The claims also cover the general process of obtention of the amido-amino acids, which includes the reaction mentioned above.

1.4.1. Comparative study of D3 and the present application

Further to the assertion of novelty made by the Examiner in connection with D3, the following arguments are added:

Both documents describe the obtention of the quinapril benzyl ester through the condensation of an N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine with a salt of the (S)-1,2,3,4-tetrahydroisoquinoline carboxylic acid benzyl ester; but following a different procedure:

1. in D3, the N-carboxyanhydride is not isolated, whereas it is used as a solid in the present application,
2. D3 starts with the (S)-1,2,3,4-tetrahydroisoquinoline carboxylic acid monotartrate benzyl ester, whereas in the present application it is started with the p-toluensulfonate,
3. In D3 there is a THF solution at 0°C, over which the benzyl ester is added; whereas in the current application one has a toluene solution of the N-carboxyanhydride at room temperature,
4. In D3 the reaction lasts overnight; whereas in the present application it lasts 4 hours and
5. In D3 the yield of the desired amide is 56%; whereas in the present application the yield of the quinapril benzyl ester is of 98 %.

Although in claim 13 of D3 the obtention of the quinapril benzyl ester and the quinapril hydrochloride are included in a general mode, it is evident that according to what is disclosed in the specification and examples the processes are different, and that the process described by the current application and illustrated through examples 1 and 2, is not claimed in D3. Furthermore, the current application does not claim the formation of the benzyl ester, but only that of the hydrochloride.

Example 18.B of document D3 and the example of the present application for the formation of the quinapril hydrochloride only coincide in the use of the hydrogenolysis catalyst, which is Pd/C. Moreover, the following differences can be established:

In the current application:

- the quinapril benzyl ester is treated with alcohol and hydrochloric acid,
- the Pd/C catalyst is added and the hydrogenation occurs at 10^5 Pa and room temperature,
- the alcohol is distilled off and toluene is added (twice),
- a solid precipitates which is the toluene solvate, which is treated with a class 3 solvent and then dried under vacuum at 40 °C;

In example 18.B of D3:

- ethanol is added to the benzyl carboxylate,
- Pd/C catalyst is added and the hydrogenation is carried out,
- filtration under vacuum is carried out,
- concentrated HCl and ether are added and
- lyophilization and washing with ether of the obtained hydrochloride powder are performed.

Therefore it is obvious that both processes have no common features with the exception of the use of Pd/C.

2. Comments on the inventive step (Part 3 of the written opinion)

To point a: point a was already commented in the foregoing section

To point b: the problem to which the present application is faced, is not only to avoid the use of acetonitrile, but also the use of DCC as a condensation agent and the solution of problems derived from the use of DCC, and therefore it is not true that the disclosure of a process free of acetonitrile as that of D1 deprives the present application of inventive; since this application solves different problems, and such problems are in addition solved through a different process and through the obtention of new products

To points c and d: these points were commented jointly with point **b**. The problem underlying the invention is not only to avoid acetonitrile and therefore the solution is not obvious. (See also comments to point **e** below).

To point e: It is not true that comparable data showing the advantages of the quinapril hydrochloride prepared according to the process disclosed in the present application over others pertaining to the state of the art do not exist, as it is evident that with the absence not only of acetonitrile but also DCC an important improvement is achieved with the possibility of obtaining quinapril in industrial scale avoiding purification problems inherent to the ureas removal for example. Moreover, there exist quantitative data of the yield obtained which are directly comparable: for example, in the preparation of the quinapril benzyl ester, in example 1 of the present application a yield of 98 % is achievedand the maleate is obtained with a purity of 99.3 %, whereas in D1, a yield of 61 % is obtained, which is supposed to be the yield of the benzyl ester and which is clearly much lower than the yield of the present application, as the maleate will supposedly be obtained with a quantitative yield in both cases. It should be also stressed that the toluene solvate is obtained with a 88 % yield and the methyl acetate as well as the ethyl formate are both obtained with a yield of 95 %. Another important aspect is that in the present application it is not necessary to isolate the quinapril benzyl ester. In preceding sections (in particular 1.4.1.) of this document there are as well directly comparable data about temperatures and reaction (or drying) time periods which are doubtless directly comparable data which show the advantages of the current invention. Therefore there exist quantitative comparable data which confirm the advantages of the present application.

To point f: not only the choice of solvents produces a new effect which is the possibility of obtaining quinapril hydrochloride with a purity of 99.8 % the possibility of obtaininsg quinapril hydrochloride dry and wihout degradation, objective that had not been achieved with other quinapril hydrochloride solvates; but also the obtention process of quinapril hydrochloride has been improved through the absence of DCC in the condensation reaction. Therefore, is obvious that the solvates obtained in the present application are new, and that their obtention process involves inventive height

To point g: it is not true that xylene is used in D1, but in D2. Furthermore, a xylene solvate is not described, and therefore, the behaviour of the supposed xylene solvate may not be extrapolated to the toluene solvate obtained in the present application.

To point h: the surprising effect achieved by the use of toluene has been commented in the preceding point **f**, and it consists of obtaining an appropriate intermediate for the ulterior purification of quinapril hydrochloride without the decomposition risk. To this purpose ethyl formate or methyl acetate are added producing thereby a solvent exchange and the new solvate obtained can be dried in the oven yielding the quinapril hydrochloride with a 99.8 % of purity. Xylene, which boiling point lies between 138°C and 144°C, depending on the isomer, would be more difficult to remove through whatever drying process. Furthermore, the drying temperature is carefully selected due to the danger of formation of the diketopiperazine derived from quinapril and therefore the selection of toluene is essential for the success of the process. On the other side, it is a question of common sense that a skilled person will preferrably use toluene over xylene because of the simple argument based on the poiling point difference, as toluene boiling point is almost 30°C below that of xylene.

It may be concluded that from the teachings of D1, D2 and D3 the object of the present invention can not be achieved, as the manner according to which the quinapril benzyl ester is prepared is different from that disclosed in D1 and D3. Furthermore, D2

does not make any contribution to the preparation of said compound. The differences in the obtention of quinapril hydrochloride are substantial with respect to the three patents quoted. It may not be concluded that from the fact that D2 uses xylene, it results obvious that by using toluene a solvate will be produced with the characteristics of that obtained in the present application, and furthermore, the xylene solvate has not been characterized in D2. Moreover xylene, even being of similar structure than toluene, behaves quite differently, for example the boiling point is substantially higher, and therefore the supposed xylene solvate has not necessarily to be similar (and will not behave similarly) to the toluene solvate.

Neither may be concluded that from the use of a condensation reaction between similar starting products - as in D3 and the present application- , and combining the use of said reaction with the use of toluene instead of xylene (according to D2) the object of the current application will be achieved without inventive activity.

3. Claims amendments (Part 4 of the written opinion)

To first and second paragraphs: claim 1, according to the Examiner's opinion will be modified to include the drying conditions and the treatment of the sample previous to the hydrogenolysis step.

Therefore the new draft of step e) will be:

"e): drying the solvate obtained in step d) at a temperature between 40 and 50 °C".

And step a) will be drafted as follows:

"a) treatment of the quinapril ester (II) where Bz is the benzyl radical, with alcohol and hydrochloric acid or hydrogen chloride and hydrogenation of same through the addition of an appropriate hydrogenation catalyst".

To the third paragraph: In our opinion it is not necessary to delete claim 9; but a more precise datum of the stoichiometric relationship will be given; therefore according to the Examiner's opinion it is modified, so that the new draft is: *"...is equal or greater in a proportion of 1.1 (benzyl ester of quinapril (II)) to 1 (hydrochloric acid) with respect to the stoichiometric one".*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ES 98/00145

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D 217/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS, CIBEPAT, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4761479 A (GOEL) 2 August 1988 (02.08.88) claim 1	1
A	US 4344949 A (HOEFLE) 17 August 1982 (17.08.82) claims 1,4 and 10; example 2	1
A	BE 892552 A (USV PHARM. CORPORATION) 20 September 1982 (20.09.82) claim 13	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1998 (03.09.98)	21 September 1998 (21.09.98)
Name and mailing address of the ISA/ S.P.T.O. Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

EL 386266139US

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/ES 98/00145

Patent document cited in search report	Publication date	Patent familiy member(s)	Publication date
US 4761479 A	02.08.1988	KR 9607087 A	27.05.1996
		EP 285992 A	12.10.1988
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		JP 57165355 A	12.10.1982

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
98133		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES98/00145	25/05/1998	29/05/1997
International Patent Classification (IPC) or national classification and IPC		
C07D217/26		
Applicant		
ESTEVE QUIMICA, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/12/1998	16.09.99
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Howarth, C Telephone No. +49 89 2399 8207

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/ES98/00145

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-18	as originally filed				

Claims, No.:

15-22	as originally filed				
1-14	as received on	16/07/1999	with letter of	12/07/1999	.

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re: I

In the new structural formulae of claim 1 the oxo groups have been omitted, for which no basis can be found.

The amendment to claim 1 part e) also appears to have no basis since the range of 40-50 °C appears to relate only to the ethyl formate and methyl acetate solvates (see p.9).

No basis can be found in the originally filed documents for the amendment to claim 9.

This report has therefore been established as if the above amendments had not been made.

Re: V

1. Cited Documents

D1 = US-A-4 344 949
D2 = US-A-4 761 479
D3 = BE-A-0 892 552

The written opinion referred to the above documents in the order they are given in the International Search Report. The numbering given above (which is retained) erroneously exchanged the first two documents, thus US-A-4 761 479 was referred to as D1. The discrepancy appears to have been detected by the Applicant as evidenced by the comment regarding inventive step (To point g).

2. Novelty

The process of the application differs from that of:
- **D2** in that the second solvate may not be formed using acetonitrile.
- **D1** and D3 in that one solvate is converted into another solvate.

The specific solvates of claims 18-22 are not disclosed in D1-D3.

Novelty is therefore acknowledged.

3. Inventive Step

a. The closest prior art is given by **D2** which discloses a similar process for the synthesis of compounds of formula (I) differing essentially only in the choice of solvents used to form the first and second solvates.

b. The problem underlying the invention would appear to be one of providing an alternative process for the synthesis of the hydrochloride salt of quinapril which overcomes the drawbacks of the prior art processes (see p.4).

c. The main drawback referred to regarding D2 is the use of the carcinogenic solvent acetonitrile.

d. The proposed solution involves the formation of a solvate with a "solvent belonging to class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying without degrading the quinapril hydrochloride".

e. If the problem is one of avoiding the use of acetonitrile, then the solution, namely of not using acetonitrile, but using a different suitable solvent, is considered obvious and an inventive step cannot be acknowledged. The definition is further clearly a definition by the effect to be achieved.

f. Regarding the comments of the Applicant's letter of 12.7.99 with respect to D2 (point 1.3.1 part 2.) : The formation of the hydrochloride salt from the benzyl ester involving H_2 and Pd/C cannot contribute to an inventive step, since this type of debenzylation is already known (e.g. from D1, Example 1). Further, the xylene solvate is isolated (see D2, column 4, line 20).

g. Since it has not been shown that using toluene to form the first solvate as opposed to xylene, as in D2, is technically relevant or that using ethyl formate or methyl acetate as opposed to acetonitrile results in any surprising effect an inventive step cannot be acknowledged for the intermediates either.

Re: VIII

1. Clarity

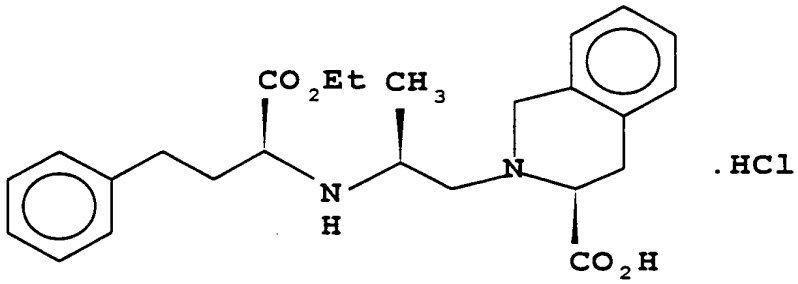
a. The term "slightly greater" in claim 9 is unclear. Also, the phrasing "can be" has no limiting effect on the scope of the claim. There appears to be no indication in the description of precisely what is meant by the term.

b. The term "hydrogenolysis" appears to be used to mean catalytic debenzylation in conjunction with hydrochloride salt formation. This is not immediately clear.

c. The term "class 3 solvent" is not clear in and of itself.

CLAIMS

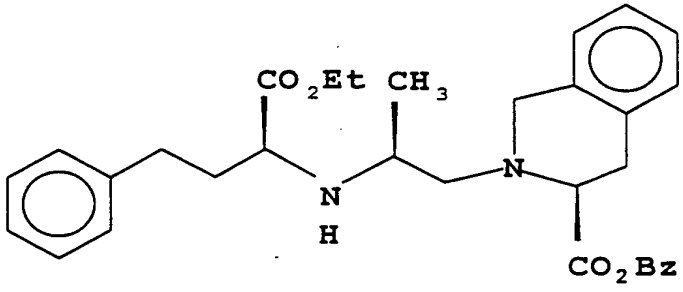
1. A process for obtaining quinapril hydrochloride of formula (I)



(I)

which comprises the stages of:

a) treatment of the benzyl ester of quinapril (II)



(II)

where Bz is the benzyl radical, with alcohol and hydrochloric acid or hydrogen chloride and hydrogenation of same through the addition of an appropriate hydrogenation catalyst;

b) removal of the solvent used in step a);

c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and

e) drying of the solvate obtained in step d) at a temperature between 40°C and 50°C to yield quinapril hydrochloride (I).

2. A process according to claim 1 wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out in a alcoholic solvent, with treatment with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, and hydrogenation with hydrogen gas in the presence of a hydrogenation catalyst.

3. A process according to claim 2, wherein said alcoholic solvent is chosen from between ethanol or isopropanol.

4. A process according to claim 2, wherein the hydrogenation is carried out at a pressure comprised 10^4 Pa and 2×10^5 Pa.

5. A process according to claim 2, wherein the hydrogenation is carried out at a temperature comprised 10 and 40°C.

6. A process according to claim 2, wherein the hydrogenation catalyst is Pd/C.

7. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of 1 x 10^5 Pa (1 bar) and room temperature.

8. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using isopropanol as a solvent, a

solution of hydrogen chloride in isopropanol, a pressure of 2 x 10^5 Pa (1 bar) and a temperature of approximately 30 °C.

9. A process according to claim 2 wherein the molar ratio between the benzyl ester of quinapril (II) and the hydrochloric acid can be equal or greater in a proportion of 1.1 (benzyl ester of quinapril (II)) to 1 (hydrochloric acid) with respect to stoichiometric one.

10. A process according to claim 1, wherein the removal of the solvent used in stage a) is carried out by vacuum-distillation.

11. A process according to claim 1, wherein the Class 3 solvent used to treat the toluene solvate of quinapril hydrochloride is chosen from among ethyl formate and methyl acetate.

12. A process according to claim 1, wherein the treatment of the toluene solvate of quinapril hydrochloride with the class 3 solvent is carried out at a temperature comprised between 40°C and 45°C, for a period of time comprised between 1 and 2 hours, and is subsequently cooled down to a temperatue comprised between 20 °C and 25 °C, for a period of time comprised between 1 and 2 hours.

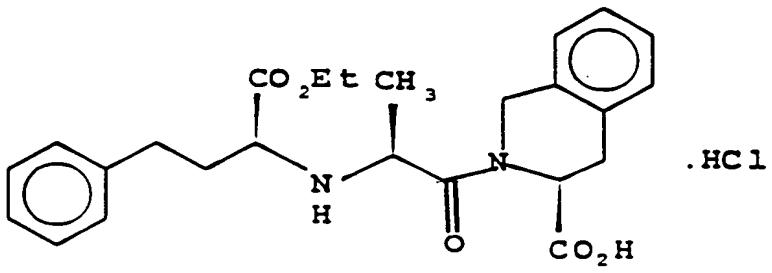
13. A process according to claim 1, wherein the Class 3 solvent solvate of quinapril hydrochloride is chosen from among ethyl formate solvate of quinapril hydrochloride and the methyl acetate solvate of quinapril hydrochloride.

14. A process according to claim 1, wherein the Class 3 solvent solvate of quinapril hydrochloride is dried in a vacuum oven , at a temperature comprised between 40 and 50 °C for a period of time comprised between 12 and 24 hours.

NEW AMENDED CLAIMS

CLAIMS

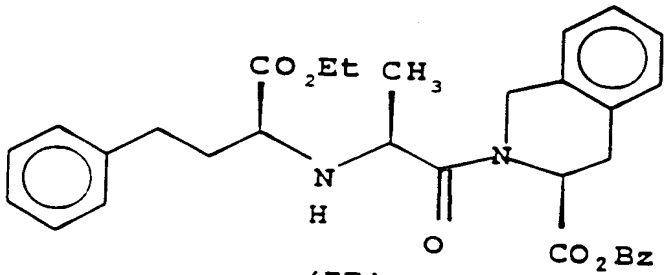
1. A process for obtaining quinapril hydrochloride of formula (I)



(I)

which comprises the stages of:

a) hydrogenolysis of the benzyl ester of quinapril (II)



(II)

where Bz is the benzyl radical;

b) removal of the solvent used in step a);

c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to Class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and

e) drying of the solvate obtained in step d) to yield quinapril hydrochloride (I).

2. A process according to claim 1 wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out in an alcoholic solvent, with treatment with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, and hydrogenation with hydrogen gas in the presence of a hydrogenation catalyst.

3. A process according to claim 2, wherein said alcoholic solvent is chosen from between ethanol or isopropanol.

4. A process according to claim 2, wherein the hydrogenation is carried out at a pressure comprised between 10^4 Pa and 2×10^5 Pa.

5. A process according to claim 2, wherein the hydrogenation is carried out at a temperature comprised between 10 and 40 °C.

6. A process according to claim 2, wherein the hydrogenation catalyst is Pd/C.

7. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of 10^5 Pa (1 bar) and room temperature.

8. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using isopropanol as a solvent, a solution of hydrogen chloride in isopropanol, a pressure of

2×10^5 Pa (2 bar) and a temperature of approximately 30 °C.

9. A process according to claim 2, wherein the molar ratio between the benzyl ester of quinapril (II) and the hydrochloric acid can be equal or slightly greater to the stoichiometric one.

10. A process according to claim 1, wherein the removal of the solvent used in stage a) is carried out by vacuum-distillation.

11. A process according to claim 1, wherein the Class 3 solvent used to treat the toluene solvate of quinapril hydrochloride is chosen from among ethyl formate and methyl acetate.

12. A process according to claim 1, wherein the treatment of the toluene solvate of quinapril hydrochloride with the Class 3 solvent is carried out at a temperature comprised between 40 °C and 45 °C, for a period of time comprised between 1 and 2 hours, and is subsequently cooled down to a temperature comprised between 20 °C and 25 °C, for a period of time comprised between 1 and 2 hours.

13. A process according to claim 1, wherein the Class 3 solvent solvate of quinapril hydrochloride is chosen from among ethyl formate solvate of quinapril hydrochloride and the methyl acetate solvate of quinapril hydrochloride.

14. A process according to claim 1, wherein the Class 3 solvent solvate of quinapril hydrochloride is dried in a vacuum oven, at a temperature comprised between 40 and 50 °C, for a period of time comprised between 12 and 24 hours.

15. A process according to claim 1, wherein the hydrogenation of the product resulting after the addition of hydrochloric acid or hydrogen chloride to the benzyl ester of quinapril (II) in stage a), is carried out without prior isolation of the intermediate formed.

16. A process according to claim 1, wherein the benzyl ester of quinapril (II) is obtained by condensation of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl -3-phenylpropyl]- L-alanine and of the benzyl ester of (S)-1,2,3,4- tetrahydro -3- isoquinolinecarboxylic acid, followed by hydrogenation in an acid medium.

17. A process according to claim 16, wherein the benzyl ester of quinapril (II) obtained is used without prior isolation.

18. A toluene solvate of quinapril hydrochloride characterised in that its infrared spectrum presents the following peaks:

IR (KBr) (ν, cm^{-1}) : 3520, 3026, 3003, 2928, 2802, 1755, 1742, 1711, 1646, 1558, 1538, 1495, 1455, 1203, 758, 737.

19. An ethyl formate solvate of quinapril hydrochloride characterised in that its X-ray diffraction pattern presents the following characteristics:

X-Ray Diffraction (powder)

Ethyl formate solvate of quinapril hydrochloride

Angle ($2\theta°$)	Relative intensity (%)
8,82	32,7
10,88	23,3

11,47	20,9
12,05	16,5
13,63	34,4
15,89	12,5
16,08	17,2
16,48	27,4
16,85	32,7
18,05	10,4
18,42	17,8
18,68	24,6
19,52	50,7
19,75	33,2
20,11	45,3
21,20	36,6
21,86	100,0
23,07	15,3
23,59	30,1
24,50	42,5
26,66	14,5
27,16	22,7
27,45	10,6
28,34	13,1
28,71	15,6
29,66	29,5
30,56	14,5
34,87	13,5

20. An ethyl formate solvate of quinapril hydrochloride according to claim 19, characterised in that its infrared spectrum presents the following peaks:

IR (KBr) (ν, cm^{-1}) : 3520, 3028, 3001, 2979, 2935, 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388, 1260, 1199, 756.

21. A methyl acetate solvate of quinapril

hydrochloride characterised in that its X-ray diffraction pattern presents the following characteristics:

X-Ray Diffraction (powder)

Methyl acetate solvate of quinapril hydrochloride

Angle (2θ°)	Relative intensity (%)
8,86	26,0
10,95	26,0
11,79	19,2
13,73	45,9
16,18	18,2
16,57	37,7
16,87	60,4
18,76	18,6
18,93	18,6
19,59	33,2
20,16	81,9
20,91	19,2
21,56	30,7
21,93	100,0
22,18	28,7
23,22	14,6
23,65	35,4
24,62	52,6
27,17	34,0
28,51	16,6
28,93	22,9
30,69	21,6
30,85	14,0

22. A methyl acetate solvate of quinapril hydrochloride according to claim 21, characterised in that its infrared spectrum presents the following peaks:

IR (KBr) (ν, cm^{-1}) : 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.